Telomere shortening and loss of self-renewal in dyskeratosis congenita induced pluripotent stem cells.

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Public Summary:
This manuscript reports, to our knowledge, the first phenotype (difference) associated with a disease, in induced pluripotent stem cells in the undifferentiated state. The cells from patients with dyskeratosis congenita, a severe and lethal condition, that is characterized by defects in chromosome telomeres (ends) were reprogrammed and assessed for defects that ranged from interaction of key proteins to inability to maintain chromosome ends (telomeres). The work indicates that induced pluripotent stem cells recapitulate key features of the disease dyskeratosis congenita and thus are a useful model to study, and potentially derive treatments for, this disorder.

Scientific Abstract:
The differentiation of patient-derived induced pluripotent stem cells (iPSCs) to committed fates such as neurons, muscle and liver is a powerful approach for understanding key parameters of human development and disease. Whether undifferentiated iPSCs themselves can be used to probe disease mechanisms is uncertain. Dyskeratosis congenita is characterized by defective maintenance of blood, pulmonary tissue and epidermal tissues and is caused by mutations in genes controlling telomere homeostasis. Short telomeres, a hallmark of dyskeratosis congenita, impair tissue stem cell function in mouse models, indicating that a tissue stem cell defect may underlie the pathophysiology of dyskeratosis congenita. Here we show that even in the undifferentiated state, iPSCs from dyskeratosis congenita patients harbour the precise biochemical defects characteristic of each form of the disease and that the magnitude of the telomere maintenance defect in iPSCs correlates with clinical severity. In iPSCs from patients with heterozygous mutations in TERT, the telomerase reverse transcriptase, a 50% reduction in telomerase levels blunts the natural telomere elongation that accompanies reprogramming. In contrast, mutation of dyskerin (DKC1) in X-linked dyskeratosis congenita severely impairs telomerase activity by blocking telomerase assembly and disrupts telomere elongation during reprogramming. In iPSCs from a form of dyskeratosis congenita caused by mutations in TCAB1 (also known as WRAP53), telomerase catalytic activity is unperturbed, yet the ability of telomerase to lengthen telomeres is abrogated, because telomerase mislocalizes from Cajal bodies to nucleoli within the iPSCs. Extended culture of DKC1-mutant iPSCs leads to progressive telomere shortening and eventual loss of self-renewal, indicating that a similar process occurs in tissue stem cells in dyskeratosis congenita patients. These findings in iPSCs from dyskeratosis congenita patients reveal that undifferentiated iPSCs accurately recapitulate features of a human stem cell disease and may serve as a cell-culture-based system for the development of targeted therapeutics.